UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,829	06/02/2006	Olivier Bezencon	AC-05-US	7180

50446 7590 07/26/2007

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,829	BEZENCON ET AL.	
	Examiner	Art Unit	
	Jeffrey H. Murray	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-16* is/are pending in the application.

4a) Of the above claim(s) *12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to a response to a restriction requirement filed on June 8, 2007. Applicants' election of Group II is acknowledged. The applicant has selected their election expressly with traverse. There are sixteen claims pending and thirteen under consideration. Claim 13 has been cancelled. Claims 12 and 14 are withdrawn from consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. This is the first action on the merits. The application concerns some novel diazabicyclononene derivatives of the general formula (I), processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as rennin inhibitors in cardiovascular events and renal insufficiency.

2. Applicant was correct in its assumption that "W" was meant in place of "Y". Applicants have also asked that the "L is not hydrogen" proviso be shifted to Group III. This will be permitted thus allowing L to be hydrogen in the elected Group II.

3. Applicant argues that the subject matter of the Groups are closely related and therefore should be examined together. This argument is found to not be persuasive. The groups should not be examined together because there is no special technical feature of the compound or composition of formula (I). Claim 1 shows a compound of formula (I) with a common feature of having a diazabicyclononene core with various substitutents. These substitutents range from single atoms to large aryl and heteroaryl groups. Therefore, these residue groups do not show any special technical feature. The core compound was seen in the prior art as explained in the

restriction requirement. Applicant's argument is not found persuasive. The restriction requirement is deemed proper and therefore made FINAL.

Priority

4. Acknowledgment is made of Applicant's claim for foreign priority. This application is a non-provisional application 10/581,829, filed June 2, 2006 and is a national stage entry of PCT/EP04/13578, filed November 30, 2004.

Specification

5. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

6. The disclosure is objected to because of the following informalities:

The specification on page 8-9 is vague and indefinite. The specification defines the term "heteroaryl" on page 8-9 by using the word "heteroaryl" in its definition (page 9, line 1). This is not permitted. Appropriate correction is required. No new matter is permitted.

7. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 1-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific compounds listed within Claim 10, 15 and 16 does not reasonably provide enablement for all the various compounds and compositions listed within Claims 1-9 and 11. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

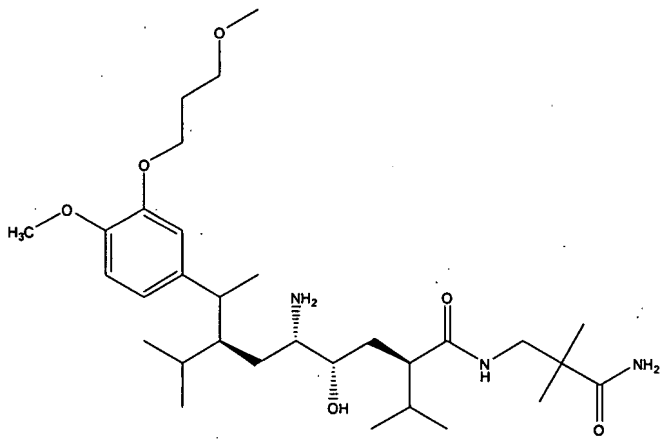
The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Many of the currently available drugs for alleviating the adverse effects of the functioning of the renin-angiotensinogen system are unsatisfactory for one reason or another. Efficacy of the drugs is often unpredictable, and unwanted side effects, due to a multiplicity of biological activities in addition to that intended, are frequent. Also, many drugs intended to reduce hypertension cannot be administered orally. This is particularly true with renin inhibitors, many of which have been shown to be active in lowering blood pressure in both animals and humans when administered intravenously or intramuscularly but are not orally active. (Almquist et. al.; US 5,268,361, p.1, col.1, para.4) Only one rennin inhibitor drug, Aliskiren, marketed under the name Tekturna®, was recently approved by the FDA (2007).

Aliskiren has a completely different structural formula as can be seen below (Whitworth et. al. p.385, Fig.3):



Morphological forms of the compound, or "polymorphs" are the ability of a substance to exist in two/more crystalline phases that have different arrangement and/or conformation of molecules in a crystal lattice.

Screening of pharmaceuticals early on in drug discovery to find out all possible solid forms has significant connotations. (Chawla et. al.; p. 9, col.2, para.1) When designing formulations, it is imperative to know which crystal form of a drug is present at the various stages of a process. "It may be possible that if one polymorph of an active pharmaceutical ingredient, or API, is responsible for activity, another form may be less active, inactive, toxic, or have some other properties of interest." (Chawla et. al.; p. 9, col.2, para.3)

Polymorphs can exhibit many types of differences in their physical properties such as a) packaging; b) thermodynamic; c) spectroscopic; d) kinetic; e) surface; and, f) mechanical properties. (Chawla et. al.; See Table 1, p. 10) These properties offer scientists the opportunity to manipulate bioavailability. It is important to determine if there are phase transformations

occurring during processing as well as what crystal form is present in the final drug product. (Newman et. al.; p. 898, col.2, Para.3)

2) *Amount of guidance provided by Applicant.* While the Applicant has demonstrated within the application how to make the compounds of Formula I, the applicant has not shown any useful data or guidance that would define a particular polymorph that would be biologically active. The applicant has inferred that any "morphological forms of the compound" would be acceptable. This can clearly not be the case. A contrasting example to this would be chloramphenicol palmitate (CAP). CAP exists in a form A and B. The metastable "form B" of CAP has an eight-fold higher bioactivity than "form A." Yet if "form B" is administered to humans, it can cause potentially fatal side effects. (Chawla et. al.; p. 9-10). Also a variety of dosage forms are available for pharmaceutical products. (Newman et. al.; p. 899, col.2, Box 1) A polymorph can affect the key solid-state parameters. For example, the drug substance in a tablet formulation will be significantly different than those for an oral suspension or inhalation product. (Newman et. al.; p. 898, col.2, Para.1)

3) *Scope of the claims.* The scope of the claims covers numerous Markush groups in Formula I such as T, Q, M, V and U, thus, the scope of claims is very broad.

4) *Number of working examples.* Applicant has only provided the names of two final compounds synthesized in this application. This is a small number considering the millions of compounds that can be synthesized due to the large Markush groups mentioned above.

5) *Nature of the invention.* The application relates to novel compounds of the general formula I. The invention also concerns related aspects including processes for the preparation of

the compounds, pharmaceutical compositions containing one or more compounds of formula I and especially their use as renin inhibitors in cardiovascular events and renal insufficiency.

6) *Level of skill in the art.* The artisan using Applicants invention would be a physician with a M.D. degree, and having several years of experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for using these compounds or compositions for treating the diseases mentioned.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On the second page of the claim listing, the "definition" of $R^{2'}$ appears in Claim 1 before the "use" of $R^{2'}$ and therefore appears indefinite. Applicant should move the definition of $R^{2'}$ in the claim to just before the definition of R^4 an $R^{4'}$, also on the second page of the claim listing.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-11 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bezencon et. al.; WO 2003093267 which was published on November 13, 2003. The instantly claimed compounds read on the reference compounds.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-11 and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Bezencon et. al.; U.S. Patent Publication Application No. 2005/0176700 which was published on August 11, 2005. The instantly claimed compounds read on the reference compounds.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 1-11 and 15-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Bezencon et. al.; WO2004002957 which was published on January 8, 2004. The instantly claimed compounds read on the reference compounds.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent Publication Application No. 2007/0142363, 2007/0135405 and 2007/0135406. Although the conflicting claims are not identical, they are not patentably distinct from each other because the Claim 1 of US 2007/0142363, US 2007/0135405 and US 2007/0135406 embraces the instant claim 1.

The instant claim differs from the copending claim by a more limited genus than the claim of the copending application. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus of the copending application, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus of the copending application since such compounds would have been suggested by the claims of the copending application. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. Claims 1-11 and 15-16 are rejected.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on M-F 7:30-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached at 571-272-0562 or Janet Andres can be reached at 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JHM

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600